



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 31/445, 31/415, 31/46, 31/00</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 95/27490</b> <b>(43) International Publication Date:</b> 19 October 1995 (19.10.95)
<p><b>(21) International Application Number:</b> PCT/EP95/01264</p> <p><b>(22) International Filing Date:</b> 6 April 1995 (06.04.95)</p> <p><b>(30) Priority Data:</b>            9406857.4                      7 April 1994 (07.04.94)                      GB</p> <p><b>(71) Applicant (for all designated States except AT DE US):</b> SANDOZ LTD. [CH/CH]; Lichtstrasse 35, CH-4002 Basle (CH).</p> <p><b>(71) Applicant (for DE only):</b> SANDOZ-PATENT-GMBH [DE/DE]; Humboldtstrasse 3, D-79539 Lörrach (DE).</p> <p><b>(71) Applicant (for AT only):</b> SANDOZ-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT M.B.H. [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).</p> <p><b>(72) Inventors; and</b></p> <p><b>(75) Inventors/Applicants (for US only):</b> MÜLLER, Wolfgang [CH/CH]; Im Rehwechsel 30, CH-4102 Binningen (CH). STRATZ, Thomas [DE/DE]; Purkersdorferstrasse 51, D-79713 Bad Säckingen (DE).</p> <p><b>(74) Common Representative:</b> SANDOZ LTD.; Patents &amp; Trade-marks Div., Lichtstrasse 35, CH-4002 Basle (CH).</p>		<p><b>(81) Designated States:</b> AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).</p> <p><b>Published</b>  <i>With international search report.            Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p><b>(54) Title:</b> USE OF SEROTONIN ANTAGONISTS (5HT<sub>3</sub>) FOR TREATING FIBROMYALGIA</p>		
<p><b>(57) Abstract</b></p> <p>5-HT<sub>3</sub> antagonists (e.g. tropisetron, ondansetron) are useful in the treatment of fibromyalgia.</p>		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

## USE OF SEROTONIN ANTAGONISTS (5HT<sub>3</sub>) FOR TREATING FIBRO MYALGIA

This invention relates to a new use of 5HT<sub>3</sub> antagonists.

These compounds are also referred to hereinafter as compounds of the invention.

5HT<sub>3</sub> antagonists are a class of compounds which block 5HT<sub>3</sub> receptors. Examples include compounds disclosed in Belgian patents 897117, 900425 and 901274. These compounds are described therein as being 5HT<sub>3</sub> receptor antagonists or serotonin M receptor antagonists (serotonin M receptors have been reclassified as 5HT<sub>3</sub> receptors).

Other classes of the compounds of the invention are known from e.g. European patent publications 13138A, 200444A, and 214772A and British Patent publication 2153821.

5HT<sub>3</sub> antagonists from various sources have been published for a wide variety of uses, for example for the treatment of visceral pain, migraine, vascular and cluster headache, trigeminal neuralgia, arrhythmia, serotonin-induced gastro-intestinal disorders, including emesis induced by anti-cancer agents, anxiety, stress-related psychiatric disorders, depression, cognitive disorders, social withdrawal, panic attacks, agoraphobia, lung embolism, rhinitis or serotonin-induced nasal disorders, for increasing vigilance or for treating dependency induced by dependence-inducing agents. Some have been commercially introduced for the treatment of emesis.

It has now surprisingly been found that the compounds of the invention exert a marked improvement in patients suffering from fibromyalgia, which affects the major symptoms including pain as well as the functional and vegetative disorders and lasts beyond the time of treatment.

Fibromyalgia (also known as fibrositis or generalized tendomyopathy) is a very common disease which is characterized by pains and stiffness in the various regions of the

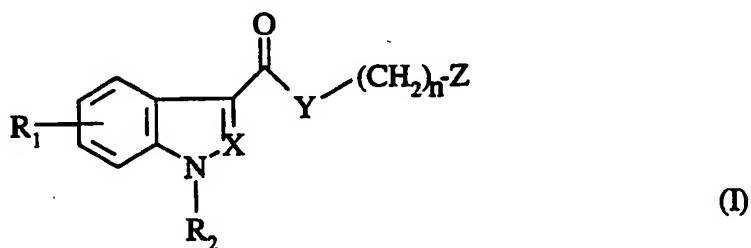
- 2 -

locomotory apparatus, particularly in the region of the tendon insertions and tendon sheaths, which are very sensitive to pressure, furthermore by functional and vegetative disorders as well as psychopathological findings such as depressive conditions and neuroses.

Examples of functional symptoms are sleep disorders, headache, migraine, globus sensation, functional breathing and cardiac complaints, gastrointestinal disorders and dysuria. Examples of vegetative symptoms are cold extremities, hyperhidrosis, dryness of mouth, dermatographia, tremor, respiratory arrhythmia and orthostatic problems.

The treatment of fibromyalgia is very problematic and unsatisfactory. An effective therapy of the disease is not available yet. Attempts to attenuate the pain symptoms using analgesics and non-steroidal anti-inflammatories were unsuccessful. Muscle relaxants showed limited activity at very high dosages which induced considerable side effects and had to be stopped. Antidepressive drugs such as amitriptyline were also proposed and showed some activity in a sub-group of patients, which however decreased rapidly.

The compounds of the invention include compounds of formula I



wherein

$R_1$  is hydrogen, halogen, hydroxy, alkoxy(1-4C), amino, alkyl(1-4C)amino or dialkyl(1-4C)amino,

$R_2$  is hydrogen, alkyl(1-7C), alkenyl(3-6C), alkynyl(3-10C), cycloalkyl(3-7C), cycloalkyl(3-7C)alkyl(1-4C), phenyl, phenylalkyl(1-3C), alkyl(1-6C)carbonyl, alkyl(1-6C)oxycarbonyl, carbamoyl, sulfamoyl or mono- or dialkyl(1-6C)-

- 3 -

carbamoyl or -sulfamoyl,

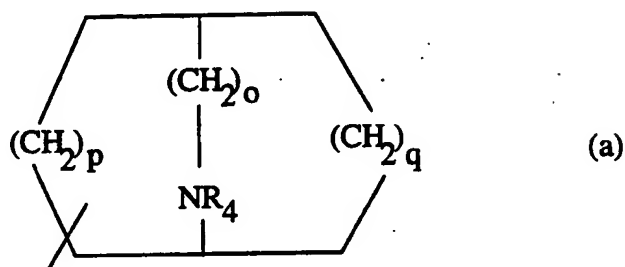
X is CH or N and

Y is  $\text{NR}_3$  or O,  $\text{R}_3$  being hydrogen or alkyl(1-6C), or

X + Y together are C-A-N or C-A-CH, wherein A is  $\text{CH}=\text{CH}$  or  $-(\text{CH}_2)_m-$ , m being 2 or 3,

n is 0, 1 or 2 and

Z is a radical of formula (a)



wherein o is 0, p is 0, 1 or 2 and q is 0, 1 or 2, or

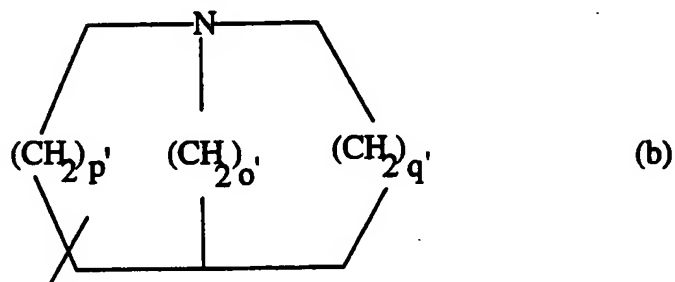
o is 1, p is 0 and q is 0 or 1, and

$\text{R}_4$  is hydrogen, alkyl(1-7C), cycloalkyl(3-6C),

phenylalkyl(1-4C) optionally mono- or disubstituted by

halogen, alkyl(1-4C) or alkoxy(1-4C),

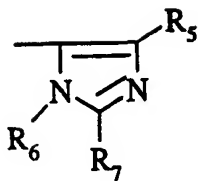
or a radical of formula (b)



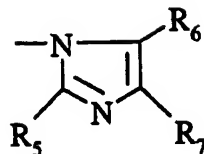
wherein  $o'$  is 1, 2 or 3,  $p'$  is 0 or 1 and  $q'$  is 0 or 1,

or a radical of formula (c) or (d)

- 4 -



(c)



(d)

wherein one of R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub> is hydrogen, alkyl(1-6C), cycloalkyl(3-7C), alkenyl(2-6C), phenyl or phenylalkyl(1-3C) and the 2 others independently are hydrogen or alkyl(1-6C), provided that Z is not (d) when n is O and Y is NR<sub>3</sub> or (with X) N-A-C,

in free form or in pharmaceutically acceptable salt or complex form.

R<sub>1</sub> is preferably hydrogen or methoxy.

R<sub>2</sub> is preferably hydrogen or alkyl(1-7C).

In R<sub>2</sub>, alkyl(1-7C) is preferably alkyl(1-4C), more preferably methyl, alkenyl(3-6C) is preferably alkenyl(3-4C), alkynyl(3-10C) is preferably alkynyl(3-4C), cycloalkyl(3-7C) is preferably cycloalkyl(3-6C), cycloalkyl(3-7C)alkyl(1-4C) is preferably cycloalkyl(3-6C)methyl, phenylalkyl(1-3C) is preferably benzyl, alkyl(1-6C)carbonyl is preferably alkyl(1-4C)carbonyl, alkyl(1-6C)oxycarbonyl is preferably alkyl(1-4C)oxycarbonyl and dialkyl(1-6C)carbamoyl and -sulfamoyl are preferably dimethylcarbamoyl and -sulfamoyl.

R<sub>3</sub> is preferably hydrogen or methyl.

R<sub>4</sub> in (a) is preferably hydrogen or alkyl(1-4C), more preferably methyl.

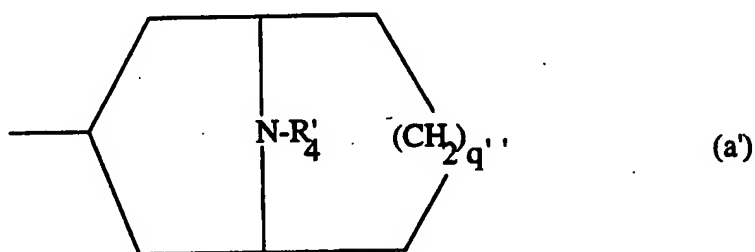
- 5 -

Preferably one of  $R_5$ ,  $R_6$  and  $R_7$  in (c) and (d) is methyl and the two others are hydrogen. More preferably  $R_5$  is methyl and  $R_6$  and  $R_7$  are hydrogen. When  $X + Y$  together are  $C-(CH_2)_m-CH$ ,  $m$  is preferably 2.

In (a) preferably  $o$  is 0 and  $p$  and  $q$  are 1 or  $p$  is 1 and  $q$  is 0.

When  $Z$  is of formula (a) or (b),  $n$  is preferably 0. When  $Z$  is of formula (c) or (d),  $n$  is preferably 1.

In a group of compounds of formula I,  $R_1$  is alkyl(1-4C),  $R_2$  is hydrogen,  $X$  is  $CH$ ,  $Y$  is  $O$  or  $NH$ ,  $n$  is 0 and  $Z$  is of formula (a')



wherein  $R'_4$  is methyl, ethyl or propyl and  $q''$  is 0, 1 or 2.

Depending on the nature of the substituents defined above, asymmetric carbons may be present in the molecule. This is the case for example when  $X + Y$  together are  $C-A-CH$ . All optical isomers and their mixtures including the racemic mixtures are part of the present invention.

Furthermore depending on the nature of the  $Y-(CH_2)_n-Z$  radical, the compounds may present the exo or endo configuration. The exo/endo nomenclature is well known in the literature. Again, both exo and endo forms and their mixtures are part of the present invention.

The endo isomers are preferred.

- 6 -

The compounds of formula I may exist in free form or in salt form. Suitable salt forms include acid addition salts and quaternary ammonium salts.

The compounds of the invention may be chosen from the following compounds:

Indol-3-yl-carboxylic acid-endo-8-methyl-8-aza-bicyclo[3,2,1]-oct-3-yl-ester (the hydrochloride is also known as tropisetron, hereinafter compound A);

benzo[b]thiophen-3-yl-carboxylic acid-endo-9-methyl-azabicyclo[3,3,1] non-3-yl-ester;

5-fluoro-1-methyl-indol-3-yl-carboxylic acid-endo-9-methyl-9-aza-bicyclo[3,3,1]non-3-yl-ester;

1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)-methyl]-4H-carbazol-4-one (also known as ondansetron; hereinafter compound B);

1-methyl-indazol-3-yl-carboxylic acid-9-methyl-9-aza-bicyclo-[3,3,1]non-3 $\alpha$ -yl-amide (also known as granisetron);

endo-4-amino-5-chloro-2-methoxy-N-(1-azabicyclo[3,3,1]non-4-yl)-benzamide;

3-[5-methyl-1H-imidazol-4-yl]-1-(1-methyl-1H-indol-3-yl)-1-propanone;

N-(1-azabicyclo[2,2,2]oct-3-yl)-6-chloro-4-methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-8-carboxamide (also known as azasetron);

N-(endo-8-methyl-8-azabicyclo[3,2,1]oct-3-yl) -2,3-dihydro-2-oxo-1H-benzimidazol-1-carboxamide;

7-methoxy-1H-indol-3-carboxylic acid-(1 $\alpha$ H,5 $\alpha$ H)-8-methyl-8-aza-bicyclo[3,2,1]oct-3 $\alpha$ -yl-ester;



- 7 -

the compound known as GR 87442.

Further preferred 5HT<sub>3</sub> antagonists include:

4,5,6,7-tetrahydro-5-[(1-methyl-indol-3-yl)carbonyl]benzimidazole;

(+)-10-methyl-7-(5-methyl-1H-imidazol-4-ylmethyl)-6,7,8,9-tetrahydropyrido[1,2-a]indol-6-one;

N-(1-ethyl-2-imidazolin-2-yl-methyl)-2-methoxy-4-amino-5-chlorobenzamide.

The unexpected efficacy of the compounds of the invention in the treatment of fibromyalgia is established in clinical trials.

In these clinical trials, ambulatory patients suffering from clinically diagnosed fibromyalgia are tested using the 10 cm visual analogue scale for patient self rating (0 = no pain; 10 = severe pain), the "pain score" (pain severity scale) at various body sites and the digital dolorimeter tenderness score at 24 tender points, according to methods described by W. Müller and J. Lautenschläger in Z. Rheumatol 49: 11-21 (1991). A tender point is a localized area of intense pain on deep palpation. Additionally the patients are asked to fill a form with respect to functional/vegetative symptoms which are evaluated as marked (3), moderate (2), mild (1) or absent (0). These symptoms include:

- cold hands or feet
- dry mouth
- increased sweating
- dizziness
- trembling
- sleep disturbances
- gastric disturbances
- intestinal disturbances, constipation/diarrhoea

- 8 -

- lumpiness in the throat
- periodic respiratory distress (without previous exertion)
- tachycardia/arrhythmia
- sleepiness, tingling or other abnormal sensations in body parts
- pain on micturation
- headache or migraine
- paresthesia

The statistical analysis of the results is effected according to the Wilcoxon test or the Mann-Whitney U-test.

In one such trial the compound of the invention was compound A and 17 patients were treated orally during 5 days, with 2x5 mg daily. Eight of those were found to be very good responders ( $\geq 40\%$  improvement in the visual analogue score), with the following results:

A significant improvement was observed in the visual analogue scale ( $p = 0.0142$ ), in the pain score ( $p = 0.014$ ), in the dolorimetry ( $p = 0.0208$  for the average pressure triggering pain and  $p = 0.0346$  for the number of tender points) and in the evaluation of the vegetative symptoms ( $p = 0.0109$ ).

In another trial with compound A, 40 patients were treated. A first group of 20 patients received 2x5 mg daily during 10 days, a second group of 20 patients received 3x5 mg daily during 10 days. Eighteen patients (9 from each group) were found to be very good responders ( $\geq 40\%$  improvement in the visual analogue score or in the pain score) with the following results:

A significant improvement was observed in the visual analogue scale ( $p < 0.0003$ , the score decreasing from 7.6 to 2.6), in the pain score (which decreased from 55.8 to 22.6) and in the dolorimetry ( $p < 0.06$  for the average pressure triggering pain, which passed from 1.91 to 2.24 kp, and  $p < 0.02$  for the number of tender points which passed from 19.4 to 14.2).

- 9 -

Also the vegetative and functional symptoms improved significantly. For example significant improvements were observed in the symptoms sleep disturbances ( $p < 0.006$ ), cold hands or feet ( $p < 0.002$ ), headaches ( $p < 0.03$ ), paresthesia ( $p < 0.008$ ), tachycardia/arrhythmia ( $p < 0.006$ ) and periodic respiratory distress ( $p < 0.006$ ).

Surprisingly in these trials the achieved improvement of both pain and vegetative symptoms lasted several weeks after therapy.

In still another trial the compound of the invention was compound B and a double-blind study was carried out with 20 patients. The patients received orally 2x8 mg/day of the compound during 5 days and after a pause of 2 days, 2x500 mg/day paracetamol during 5 days (or vice-versa depending on randomisation). Eleven patients were found to be very good responders to compound B according to the definition given above, with the following results:

A significant improvement was observed in the visual analogue scale ( $p = 0.003$ ), in the pain score ( $p = 0.022$ ), in the dolorimetry ( $p = 0.008$  for the average pressure and  $p = 0.018$  for the number of tender points) and in the evaluation of the vegetative symptoms ( $p = 0.003$ ).

Under paracetamol, no significant improvement was observed in the visual analogue scale and in the pain score. In the dolorimeter, the results were significantly negative (decrease of pressure triggering pain,  $p = 0.028$ ; increase of number of tender points,  $p = 0.029$ ).

Again, the good results achieved with compound B lasted several weeks after treatment, during which the general condition of the patients was significantly improved.

These trials are indicative for a long-lasting and disease-modifying (as opposed to merely symptomatic) activity of the compounds.

The compounds of the invention are therefore useful in the treatment of fibromyalgia.

- 10 -

For this indication the appropriate dosage will, of course, vary depending upon, for example, the compound employed, the host, the mode of administration and the nature and severity of the condition being treated. An indicated daily dosage is in the range usually used for known indications such as emesis and is typically from about 0.05 to about 50 mg, conveniently administered, for example, in divided doses up to four times a day, in unit dosage form or in sustained release form.

The compounds of the invention may be administered by any conventional route, in particular enterally, preferably orally e.g. in the form of tablets or capsules, or parenterally, e.g. in the form of injectable solutions or suspensions.

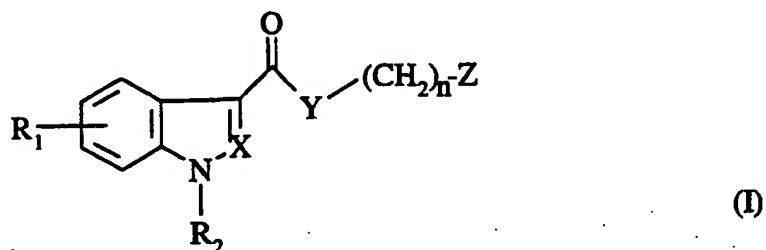
The present invention also provides pharmaceutical compositions comprising the compounds in association with at least one pharmaceutical carrier or diluent for use in the treatment of fibromyalgia. Such compositions may be manufactured in conventional manner. Unit dosage forms may contain for example from about 0.01 mg to about 25 mg of the compound.

The invention further provides the use of a compound of the invention for the manufacture of a pharmaceutical composition for the treatment of fibromyalgia.

The invention furthermore provides a method for the treatment of fibromyalgia in a subject in need of such treatment, which comprises administering to said subject a therapeutically effective amount of a compound of the invention.

CLAIMS

1. The use of a 5-HT<sub>3</sub> antagonist in the treatment of fibromyalgia.
2. The use according to claim 1 wherein the 5-HT<sub>3</sub> antagonist is of formula I



wherein

$R_1$  is hydrogen, halogen, hydroxy, alkoxy(1-4C), amino, alkyl(1-4C)amino or dialkyl(1-4C)amino,

$R_2$  is hydrogen, alkyl(1-7C), alkenyl(3-6C), alkynyl(3-10C), cycloalkyl(3-7C), cycloalkyl(3-7C)alkyl(1-4C), phenyl, phenylalkyl(1-3C), alkyl(1-6C)carbonyl, alkyl(1-6C)oxycarbonyl, carbamoyl, sulfamoyl or mono- or dialkyl(1-6C)-carbamoyl or -sulfamoyl,

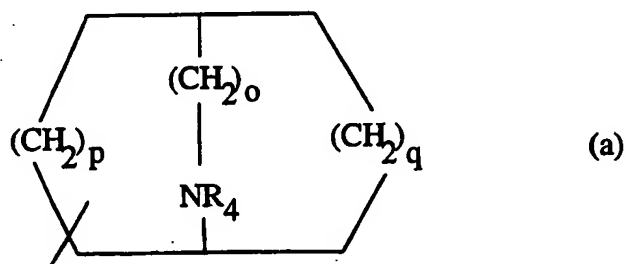
X is CH or N and

Y is  $NR_3$  or O,  $R_3$  being hydrogen or alkyl(1-6C), or

X + Y together are C-A-N or C-A-CH, wherein A is  $CH=CH$  or  $-(CH_2)_m-$ , m being 2 or 3,

n is 0, 1 or 2 and

Z is a radical of formula (a)



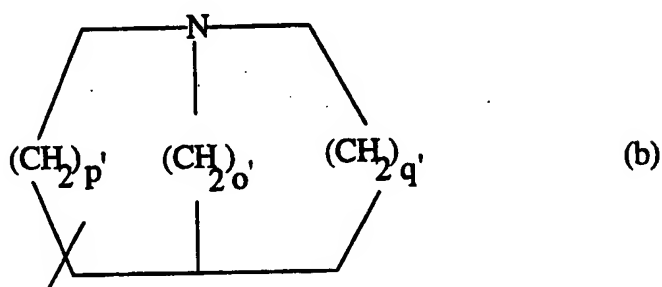
- 12 -

wherein  $o$  is 0,  $p$  is 0, 1 or 2 and  $q$  is 0, 1 or 2, or

$o$  is 1,  $p$  is 0 and  $q$  is 0 or 1, and

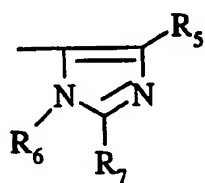
$R_4$  is hydrogen, alkyl(1-7C), cycloalkyl(3-6C),  
phenylalkyl(1-4C) optionally mono- or di-  
substituted by halogen, alkyl(1-4C) or  
alkoxy(1-4C),

or a radical of formula (b)

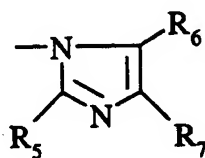


wherein  $o'$  is 1, 2 or 3,  $p'$  is 0 or 1 and  $q'$  is 0 or 1,

or a radical of formula (c) or (d)



(c)



(d)

wherein one of  $R_5$ ,  $R_6$  and  $R_7$  is hydrogen, alkyl(1-6C), cycloalkyl(3-7C),  
alkenyl(2-6C), phenyl or phenylalkyl(1-3C) and the 2 others independently  
are hydrogen or alkyl(1-6C), provided that  $Z$  is not (d) when  $n$  is 0 and  $Y$   
is  $NR_3$  or (with  $X$ )  $N-A-C$ ,

in free form or in pharmaceutically acceptable salt or complex form.

- 13 -

3. The use according to claim 1 wherein the 5-HT<sub>3</sub> antagonist is indol-3-yl-carboxylic acid-endo-8-methyl-8-aza-bicyclo[3,2,1]-oct-3-yl-ester in free form or pharmaceutically acceptable salt or complex form.
4. The use according to claim 1 wherein the 5-HT<sub>3</sub> antagonist is 1,2,3,9-tetrahydro-9-methyl-[(2-methyl-1H-imidazol-1-yl)-methyl]-4H-carbazol-4-one.
5. The use of a 5-HT<sub>3</sub> antagonist for the manufacture of a pharmaceutical composition for the treatment of fibromyalgia.
6. A method for the treatment of fibromyalgia in a subject in need of such treatment, which comprises administering to said subject a therapeutically effective amount of a 5-HT<sub>3</sub> antagonist.
7. A pharmaceutical composition which incorporates as active agent a 5-HT<sub>3</sub> antagonist for use in the treatment of fibromyalgia.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 95/01264

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/445 A61K31/415 A61K31/46 A61K31/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	ZEITSCHRIFT FUR RHEUMATOLOGIE, vol. 53, no. 6, November 1994 pages 335-338, STRATZ, SCHOCHAT ET AL 'Die Therapie der generalisierten Tendomyopathie (Fibromyalgie) durch Blockierung der 5-HT3-Rezeptoren' See Abstract --	1-7
P, Y	---	1-7
	--- -/--	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*B\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*&\* document member of the same patent family

Date of the actual completion of the international search

18 August 1995

Date of mailing of the international search report

21. 09. 95

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,  
Fax (+ 31-70) 340-3016

Authorized officer

Herrera, S



# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 95/01264

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	RHEUMATOLOGIA, vol. 32, no. 4, 1994 POLAND, pages 404-408, KLAM K., STRATZ T. ET AL 'Serum serotonin levels in patients with primary fibromyalgia treated with Tropisetron (Navoban)' See abstract	1-3,5-7
P,Y	--- ---	1-7
P,X	BR. J. RHEUM. , vol. 34, no. 3, 1995 UNITED KINGDOM, pages 283-284, BALINT G. '6TH EUROPEAN REGIONAL CONFERENCE OF REHABILITATION INTERNATIONAL' PUBLISHED ORALLY 4-9 SEPTEMBER 1994 ; see page 283, right column, line 13-28	1,2,4-7
P,Y	---	1-7
X	EP,A,0 261 964 (BEECHAM GROUP PLC) 30 March 1988 see claim 1	7
Y	---	1-7
X	EP,A,0 498 466 (BEECHAM GROUP PLC) 12 August 1992 see claim 1	7
A	EP,A,0 200 444 (BEECHAM GROUP PLC) 5 November 1986 see page 20, line 34 - page 21, line 30; claim 1	1-7

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 95/01264

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0261964	30-03-88	JP-A- 2009878 US-A- 4937247	12-01-90 26-06-90
EP-A-0498466	12-08-92	AU-B- 594670 AU-A- 5657986 CA-A- 1296004 DE-A- 3687080 DK-B- 170166 EP-A, B 0200444 IE-B- 58313 JP-C- 1798883 JP-B- 4078636 JP-A- 61275276 JP-A- 5194508 US-A- 4937247 US-A- 4886808 US-A- 5034398 EP-A, B 0223385 ES-T- 2053439	15-03-90 06-11-86 18-02-92 17-12-92 06-06-95 05-11-86 08-09-93 12-11-93 11-12-92 05-12-86 03-08-93 26-06-90 12-12-89 23-07-91 27-05-87 01-08-94
EP-A-0200444	05-11-86	AU-B- 594670 AU-A- 5657986 CA-A- 1296004 DE-A- 3687080 DK-B- 170166 EP-A- 0498466 IE-B- 58313 JP-C- 1798883 JP-B- 4078636 JP-A- 61275276 JP-A- 5194508 US-A- 4937247 US-A- 4886808 US-A- 5034398 EP-A, B 0223385 ES-T- 2053439	15-03-90 06-11-86 18-02-92 17-12-92 06-06-95 12-08-92 08-09-93 12-11-93 11-12-92 05-12-86 03-08-93 26-06-90 12-12-89 23-07-91 27-05-87 01-08-94